10/530919
PCT/GB 2003 / 0 0 4 3 5 2

1/1

PATENTS • DESIGNS • TRADE MARKS
The Patent Office

INVESTOR IN PEOPLE

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

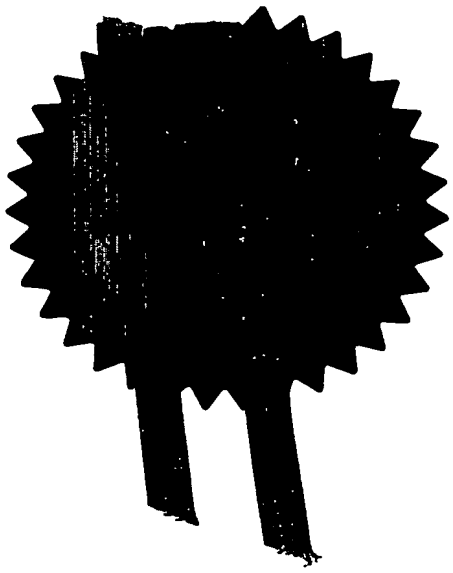
The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.



Signed Stephen Hordley

Dated 24 October 2003

Patents Form 1/77

Act 1977

The Patent Office

THE PATENT OFFICE
-8 OCT 2002
LONDON

02 E754148-3 D02094
P01/7700 0.00-0223327.8

Request for grant of a patent

1/77

The Patent Office

Cardiff Road
Newport
Gwent NP9 1RH

1. Your reference — 14 41671

2. Pater — 0223327.8

8 OCT 2002

3. Full name, address and post code of the or each applicant

Ranier Limited
Greenhouse Park Innovation Centre
Newmarket Road
Cambridge CB1 5AS

Patents ADP number

If the applicant is a corporate body, give the country/state of its incorporation — UK

T 0419160 02

4. Title of the invention — ARTIFICIAL SPINAL DISC

5. Name of your agent — VENNER, SHIPLEY & CO

"Address for service" in the United Kingdom to which all correspondence should be sent

20 LITTLE BRITAIN
LONDON
EC1A 7DH

Patents ADP — 1669004

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or each of these earlier applications and the or each application number

Country	Priority application number	Date of filing

7. If this application is divided or otherwise derived from an earlier UK application, give the number and filing date of the earlier application

Number of earlier application	Date of Filing

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'YES' if:*
a) any applicant in 3. above is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body)

YES

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	11
Claim(s)	DM
Abstract	
Drawing(s)	6 + 6

10. If you are also filing any of the following state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents	

11. I/We request the grant of a patent on the basis of this application.

Signature: Venner Shipley & Co.

Date: 8 October 2002

12. Name and daytime telephone number of person to contact in the United Kingdom

IAN GREY
020 7600 4212

Artificial Spinal Disc

Description

The present invention relates to an artificial spinal disc or disc spacer used to replace a displaced or damaged intervertebral disc in the spine of a patient. The invention also relates to a method of manufacturing a component, such as the artificial spinal disc of the invention.

Approximately one third to a quarter of the length of an adult human spine is occupied by the vertebral discs. Each disc comprises an annular wall (annulus fibrosus) that surrounds and contains a central nucleus (nucleus pulposus) filled with gelatinous material that occupies approximately 30 to 50% of the cross sectional area of the disc. The annular wall is a concentrically laminated structure containing aligned collagen fibres and fibrocartilage and provides the major stabilizing structure to resist torsional and bending forces applied to the disc. The discs are contained between vertebral endplates comprised of hyaline cartilage that act as an intermediate layer between the hard vertebrae and the softer material of the disc and facilitates smooth movement of the disc.

The joints of the human body are subject to traumatic injury and disease that over a life-time can lead to the deterioration or failure of the joint causing severe pain or immobility. Generally, the ability of a load bearing joint to provide pain free articulation and carry its load is dependent upon the presence of healthy intact cartilage within a stable joint. With reference to a vertebral joint, spinal disc degeneration such as loss of fluid, annular tears and myxomatous changes can result in herniation of the nucleus in which the disc protrudes into vertebral canal causing back pain and sciatica. This condition is more commonly referred to as a "slipped" disc.

To alleviate the condition described above, the damaged spinal disc may be surgically removed from the spine and the two adjacent vertebrae either side of the damaged disc fused together (anthrodesis). Although this technique successfully eliminates the symptoms of pain and discomfort and improves joint stability, it

results in a total loss of movement of the fused vertebral joint and increases the stress placed on the adjacent joints leading to collateral damage of these joints and associated soft tissues.

A more desirable solution is to replace the damaged spinal disc with an artificial implant (athroplasty) that allows full, pain free movement of the vertebrae and which mimics the function of a healthy spinal disc. Artificial spinal discs currently exist for use in such a procedure. However, the development of existing artificial discs has been limited, despite advances in biomaterials, because they lack the complexity of structure and cannot adequately mimic the biomechanics of a normal healthy human spinal disc.

Conventional artificial spinal discs are generally either manufactured using a material of single uniform hardness (single durometer) or using two materials of differing hardness (dual durometer), in which case the material has a lower modulus core contained within a higher modulus shell. The former requires a compromise in material specification to balance strength and wear resistance with compliance whereas the latter often generates problems caused by a progressive failure of along the interface between the two materials over a period of use. An artificial spinal disc of the latter type is known from US patent no. 5,171,281.

A need therefore remains for an artificial spinal disc implant which can be surgically inserted in place of a damaged spinal cartilage disc and which will enable full, pain-free movement of the affected vertebral joint, which is durable enough to withstand the loads and wear imposed upon it in use without failing, and at the same time exhibit biomechanics which are as similar as possible to that of the body's own natural spinal discs and so can withstand both compression and torsional loading. If these requirements are not adequately met, and the artificial disc is too stiff, it will not deform sufficiently during movement and excessive deformation of the adjacent natural discs will occur. On the contrary, if the disc does not have the required degree of stiffness, excessive movement of the disc will occur causing it to bulge out resulting in pain and discomfort for the patient.

According to the invention, there is provided an artificial spinal disc comprising a body of material having at least a portion that exhibits a gradual variation in modulus as a function of the distance from the surface of the body. This graduation in the property of the material provides an artificial disc having all the benefits of a dual material design without any of the problems associated with the bonding of two dissimilar, separate components. The disc contains and constrains excessive deformation whilst maintaining the normal physiological motions of the spinal segment.

The modulus referred to is the modulus of elasticity or tensile modulus, also referred to as Young's Modulus, and is the ratio of stress to strain below the elastic limit. The Young's Modulus is calculated by dividing the strain into stress and provides a measure of the stiffness of the material.

Preferably, the modulus varies linearly as a function of the distance from the surface of the body.

In one embodiment, the modulus varies as a function of the distance from the surface of the body in a radial direction.

The body preferably comprises a core region and a peripheral region surrounding the core.

Advantageously, the modulus of the peripheral region decreases as a function of the radial distance from the surface of the peripheral region to the core region.

Alternatively, the modulus decreases as a function of the radial distance from the surface of the body in a portion between the peripheral region and the core region.

In a preferred embodiment, the core region constitutes between 20% and 40% of the volume of the whole disc.

The disc of the present invention is preferably formed from a polymeric elastomer.

The invention also provides a method of manufacturing a component that comprises a body of material having at least a portion that exhibits a gradual variation in modulus as a function of the distance from the surface of the body, comprising the steps of diverting an output having a first predetermined thermal history from a PPM apparatus into a mould with a retractable central portion, retracting the central portion and diverting an output having a second predetermined thermal history into the mould to form a component having a variation in modulus across the boundary between the first and second outputs.

The invention also provides a further method of manufacturing a component according to the invention that comprises a body of material having at least a portion that exhibits a gradual variation in modulus as a function of the distance from the surface of the body, the method comprising the steps of simultaneously diverting the output from two separate PPM machines to a mould having two separate inputs, each output having a different predetermined thermal history, such that interfacial mixing of the outputs occurs in the mould.

Preferably, the component is an artificial spinal disc according to the invention.

Although the specification refers to an artificial spinal disc, it is envisaged that other components for medical or non-medical use could also be formed using one or other of the methods of the invention. One particular component is a catheter. Accordingly, the invention also provides a catheter comprising an elongate body of material having a longitudinal portion that exhibits a gradual variation in modulus along the length of said longitudinal portion.

Embodiments of the present invention will now be described, by way of example only, with reference to the following drawings, in which:

Figure 1 shows a perspective view of an artificial disc according to an embodiment of the invention together with endplates above and below the disc;
Figure 2 shows a plan view of the disc shown in Figure 1;

Figure 3 shows a cross-sectional view along the line X-X in Figure 2;
Figure 4 is a graph showing the relationship between the modulus and distance through the disc in a radial direction indicated by X-X;
Figure 5 is a graph showing the relationship between the modulus and the distance through the disc in a radial direction indicated by Y-Y in Figure 2;
Figure 6 is a graph showing the relationship between the modulus and the distance through the disc in an axial direction indicated by Z-Z in Figure 3;
Figure 7 illustrates a conventional reactive injection moulding apparatus with four injection lances;
Figure 8 illustrates a side view of one of the injection lances of the reaction injection moulding apparatus of Figure 7; and
Figure 9 illustrates a front view of a PPM apparatus.

Referring now to Figure 1, there is shown an artificial disc 1 together with a pair of end plates 2 used in conjunction with the disc 1. The disc 1 is a single unitary component having a soft elastomeric core region that mimics the function of the natural spinal disc nucleus and varies in volume from 20 to 40% by volume of the total elastomer volume, and a peripheral region surrounding the core region exhibiting a graded modulus structure in which the modulus increases as a function of the distance from the nucleus region or decreases as a function of the distance from the surface of the disc 1. In the preferred illustrated embodiment, the modulus varies from the surface of the disc to the nucleus. However, it will also be appreciated that the modulus may vary for only a portion of that distance. Although reference is made to a disc having a peripheral region and a core region, it will be appreciated that these regions are not separate or discrete and the disc is formed from one body of material.

Figure 2 shows a plan view of the spinal disc illustrated in Figure 1 and Figure 3 shows a cross-section through the disc along the line marked X-X in Figure 2. Both views have been marked with contour lines showing the change in modulus through the disc, the modulus being greater where the lines lie close together. As can be seen from Figure 2, the modulus increases as a function of the distance from the core region in a radial direction such as the directions indicated by X-X and Y-Y in

Figure 2, and this is shown in the plots of Figures 4 and 5. Figure 4 illustrates a plot showing the relationship between the modulus (y-axis) against distance through the disc (x-axis). In figure 4, this distance is the radial distance along the line X-X in Figure 2. In Figure 5, the distance is the radial distance along the line Y-Y in Figure 2. Figure 6 also shows the change in modulus with respect to the distance through the article in an axial direction along the line Z-Z in Figure 3. It can be seen from these graphs, that the material of the disc is anisotropic in that the modulus is different depending on the direction of measurement of the modulus through the disc.

In Figure 1, the end plates 2 are shown separated from the disc for the purpose of the drawing only and are in intimate contact with upper and lower surfaces of the disc respectively when the disc is in use. The end plates 2 are usually bonded to the disc 1. However, they can also be unbonded but in close contact with the disc 1. The end plates 2 are constructed from any suitable metallic material or alloy that possesses sufficient stiffness to contain the disc and suitable fatigue strength for that purpose. In other embodiments, the end plates 2 may be provided with a structured surface with channels and bores suitable to promote bone ingrowth. The end plates 2 may also be coated with an osteoconductive ceramic such as hydroxy apatite.

A disc 1 having the properties described above exhibits responses to compression and compression-torsion testing under simulated biomechanical loads that are similar to those exhibited by the natural spinal disc during movement of a human being and has mechanical properties (force penetration, recovery, creep) that ensures that the disc and the end plates deliver physiological appropriate motion (flexion, extension and torsion) to the adjacent vertebrae similar to those of a healthy spinal disc.

It is envisaged that the graded modulus material used to form the artificial spinal disc of the present invention could also be employed in the manufacture of other components for use in the medical and non-medical industry. A proposed alternative use, in the medical industry, is in the manufacture of an intravenous or

urethral catheter which must have the required degree of stiffness to enable it to be passed through bodily conduits to reach the site of an occlusion but at the same time be flexible enough to prevent unnecessary trauma or collateral injury to the patient during an invasive procedure. It is envisaged that at least a portion of the elongate catheter may be formed from material having a gradual variation in modulus along its length.

A method of manufacture of a component having a graded modulus, such as the artificial spinal disc of the present invention, will now be described.

Polyurethanes having a high degree of consistency making them suitable for use in the medical product industry can be manufactured using a process known as precision polyurethane manufacture (PPM). This process is described in detail in the Applicant's own earlier International Application No. PCT/GB01/03441 (Publication No. WO 02/11975), to which reference is hereby made. The methods of the present invention involve an adaptation or include the use of the aforementioned process to produce precision polymers having a graded modulus. It is also envisaged that a component having a graded modulus may be formed using a conventional Reaction Injection Moulding Machine when subsequent processing steps on the output material from such a machine are performed. Following a discussion of the PPM process, various methods of manufacture will be described.

In the PPM process, at least two reagents are intensively mixed, in a reaction injection moulding apparatus, prior to being reactively extruded, to form a polyurethane having predetermined stoichiometry and thermal history. A conventional reactive injection moulding apparatus 3 is illustrated in Figure 7 and comprises four injection lances 5, a four reagent stream mix head 6 and a mould 7. Each lance 5 is numbered for ease of identification and comprises a hydraulic cylinder 8, a lance pump 9, an inlet pipe 10, a non-return valve 11 and an outlet pipe 13. The mix head 6 is adapted so that both pairs of reagent streams from the four outlet pipes 13 directly oppose each other. The mix head 6 comprises a cylindrical mix-pin 14 having four vertical grooves (not shown) that are inscribed into the

surface of the cylinder at equal intervals and run along 3/8ths of its length from the mid point to within 1/8th of its length from the bottom face of the pin 14.

Referring to Figure 8, each lance 5 is supplied with reagent from mix tank 15 which is stirred by a paddle stirrer 16. Reagent is supplied to lance 5 via inlet pipe 10, passing through non-return valve 11. Reagent is drawn from mix-tank 15 into lance 5 by raising lance pump 9 and subsequently ejected from lance 5 by depression of lance pump 9 through the action of hydraulic cylinder 8 controlled by means of a linear transducer 17. Reagent is supplied to mix-head 6 via outlet pipes 13. When mix pin 10 is fully inserted into mix head 6, the grooves align with the outlet pipes 9 to provide channels to the return pipes 18, such that the reagent streams are recycled to mix-tanks 15 without being able to enter the mould 7. When mix-pin 10 is retracted so that its lower face sits between outlet pipes 13 and the return pipes 18 , the reagents are impingement mixed before passing into mould 7. When mould 7 is full, mix pin 10 is again fully inserted allowing excess reagents to be recycled to mix tanks 15 via return pipes 18.

Apparatus for precision polyurethane manufacture is illustrated in Figure 8. The apparatus comprises four injection lances 5, a mix head 6 and an extruder 18. The extruder 18 is joined to the mix head 6 via a rheometer 19 and has 30mm diameter co-rotating twin screws (not shown), sixteen programmable heating zones 20, a second rheometer 21 and a die 22. It will be appreciated that alternative forms of extruders can also be used depending on the application. When mix pin is retracted, mixed reagents from mix head pass via rheometer 19 into the extruder 18. Reaction mixture passes through each of the heating zones 20 which are programmed to maintain the mixture at a predetermined temperature before exiting the extruder 18.

When the apparatus is ready to run, the lances 5 eject reagents into the respective transfer lines. The velocity of each lance 5 is monitored by software and, when constant, the mix pin 14 is retracted allowing impingement mixing of the reagents in the mix head 6. The mixed reagents undergo rapid polymerisation reactions as they pass from the mix head 6 into the close coupled twin screw extruder via an in-line rheometer 19. The reacting mixture passes through the extruder 18 in a

predetermined time and follows a predetermined thermal profile dictated by the combination of the running speed of the extruder 18 and the temperature settings of each of the sixteen temperature zones 20. An in-line rheometer 21 is fitted at the output end of the extruder 18 to give real time measurement of rheological properties which are used as a signal to control aspects of the operation of the process, such as extruder speed, temperature of the extruder zones, lance speed, stoichiometry, reagent temperature, in accordance with an algorithm operated by a computer, to give real time control of the rheological properties of the polyurethane.

A first method of making an artificial spinal disc according to the present invention will now be described. In this method, known as step perturbation, the continuous flow through the extruder 18 is monitored and diverted from the extruder 18 of the PPM apparatus at a point along its length where the polyurethane is found to have the required thermal history and stoichiometry. The flow enters a two part mould so that the peripheral region is filled with the output material. Once the first part of the mould which defines the peripheral region of the artificial disc, is full, the reaction mix is changed to a material having a different thermal history and stoichiometry and, as the second desired output is formed, the flow is again diverted to the mould with the centre part of the mould, defining the core region of the artificial implant, removed or retracted to allow the complete mould to be filled. Polymerisation and cross-linking reactions continue to occur after the mould is filled causing diffusion of the two outputs across the boundary between them. As each output material has a different modulus, this diffusion creates an area within the moulded component that exhibits a graded modulus.

In a modified arrangement of the first method, the composition of the mix may be changed dynamically during filling of the mould rather than sequentially. In this case, only a portion of the flow from the extruder is diverted into the mould so that it will be filled with material formed from a continuously altered mix. This method provides a smooth gradient in modulus profile through the resulting component.

The first method described above produces an article in which only exhibits a graded modulus for a relatively thin portion of the material, although the modification of the first method may produce an article with a larger region exhibiting a variable modulus. The second method, described hereafter, can be used to manufacture an article such as a spinal disc in which the modulus varies over a wider area or from the surface of the product to the core region. In this method, known as the dual head technique, two output streams, having different compositions, from two PPM machines are fed to a mould with two separate inputs at the same time. The input ports of the mould are so arranged to cause the mould to fill in a prearranged manner so that interfacial mixing of the two streams occurs resulting in the formation of a graded modulus structure.

In yet another proposed method, the output from the reaction injection moulding machine may be continuous and of a fixed composition. However, the extruder of the PPM machine may be provided with multiple ports along its length and the mould may be filled with material sampled from each port. As the material from each port will have a different thermal history, the resultant material from each port will possess a different modulus. A layer of material from each port is fed into the mould. The layers will diffuse into each other to provide a final component having a variable modulus. The component may also undergo a post compression stage at high temperature to form the final product and increase the degree of diffusion of the layers into each other to provide a product having a more gradual change in modulus.

Although reference is made to an extruder of the PPM machine, it is also envisaged that a tube reactor may be employed instead. Alternatively, the extruder can be omitted altogether and the required formulation profile may be injected directly from the mix head of the reaction injection moulding machine into the desired shape cavity mould which is then subjected to post compression.

Alternatively, the required formulation profile may be injected from a Reaction Injection Moulding machine into an intermediate vessel such as a mould to form a slug of material which is maintained at an adequate temperature in, for example, a

temperature controlled carousel. At the required moment, a slug can be injected into a cavity mould having the shape of the required component. As the material is held in the carousel, it enables the reactant to consolidate and a known thermal history to be imparted into the product.

The intermediate vessel may alternatively be an injection moulding "syringe". The material may then be injected directly into the required mould.

Many modifications and variations of the invention will be apparent to those skilled in the art and the foregoing description should be regarded as a description of the preferred embodiments only.

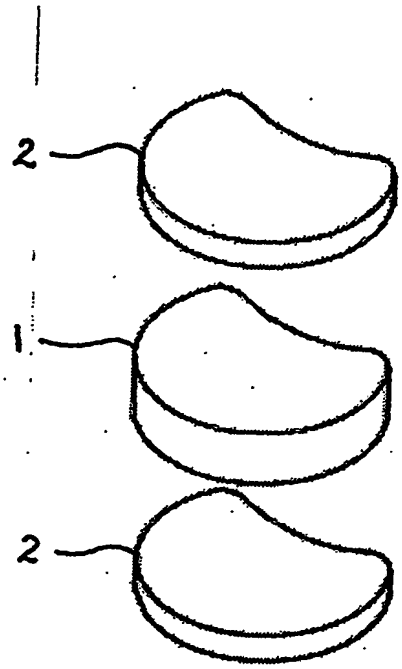


FIGURE 1

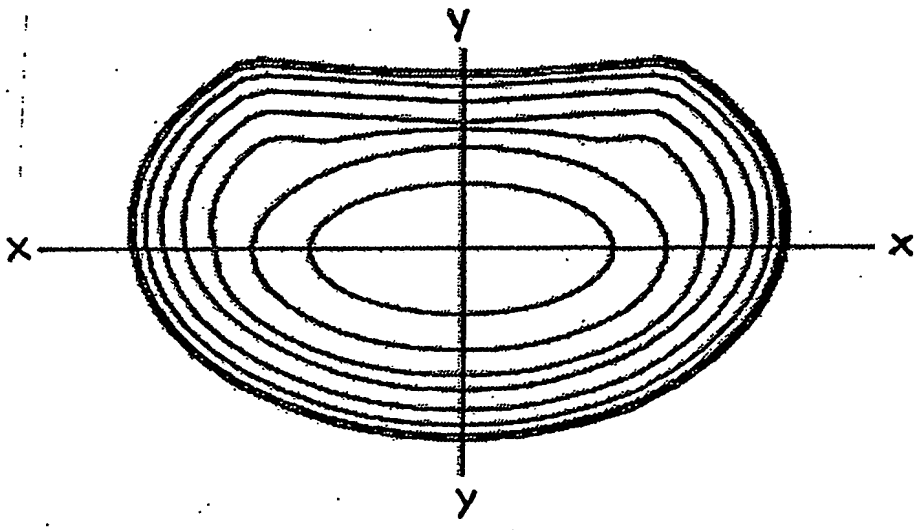


FIGURE 2

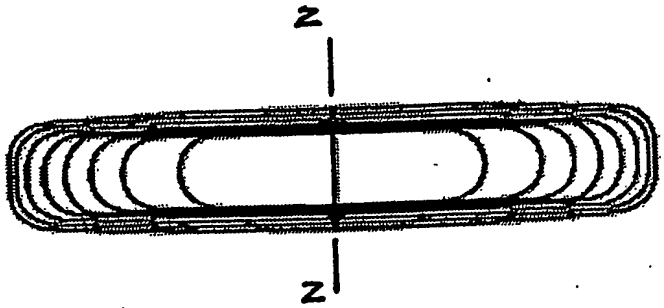


FIGURE 3

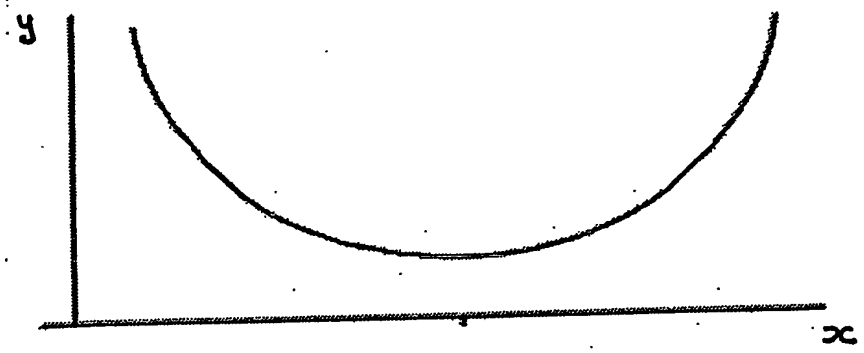


FIGURE 4

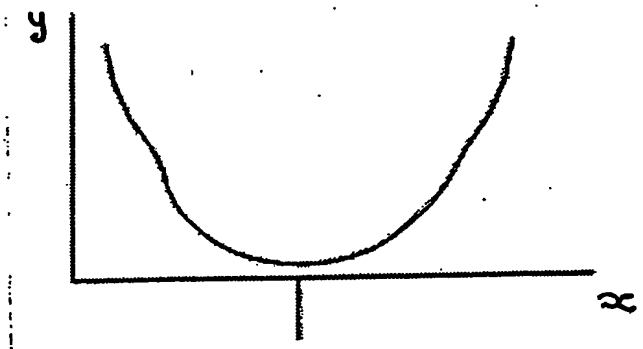


FIGURE 5

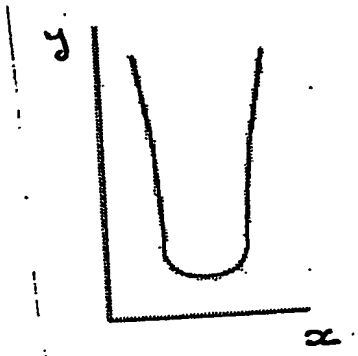


FIGURE 6

FIGURE 7

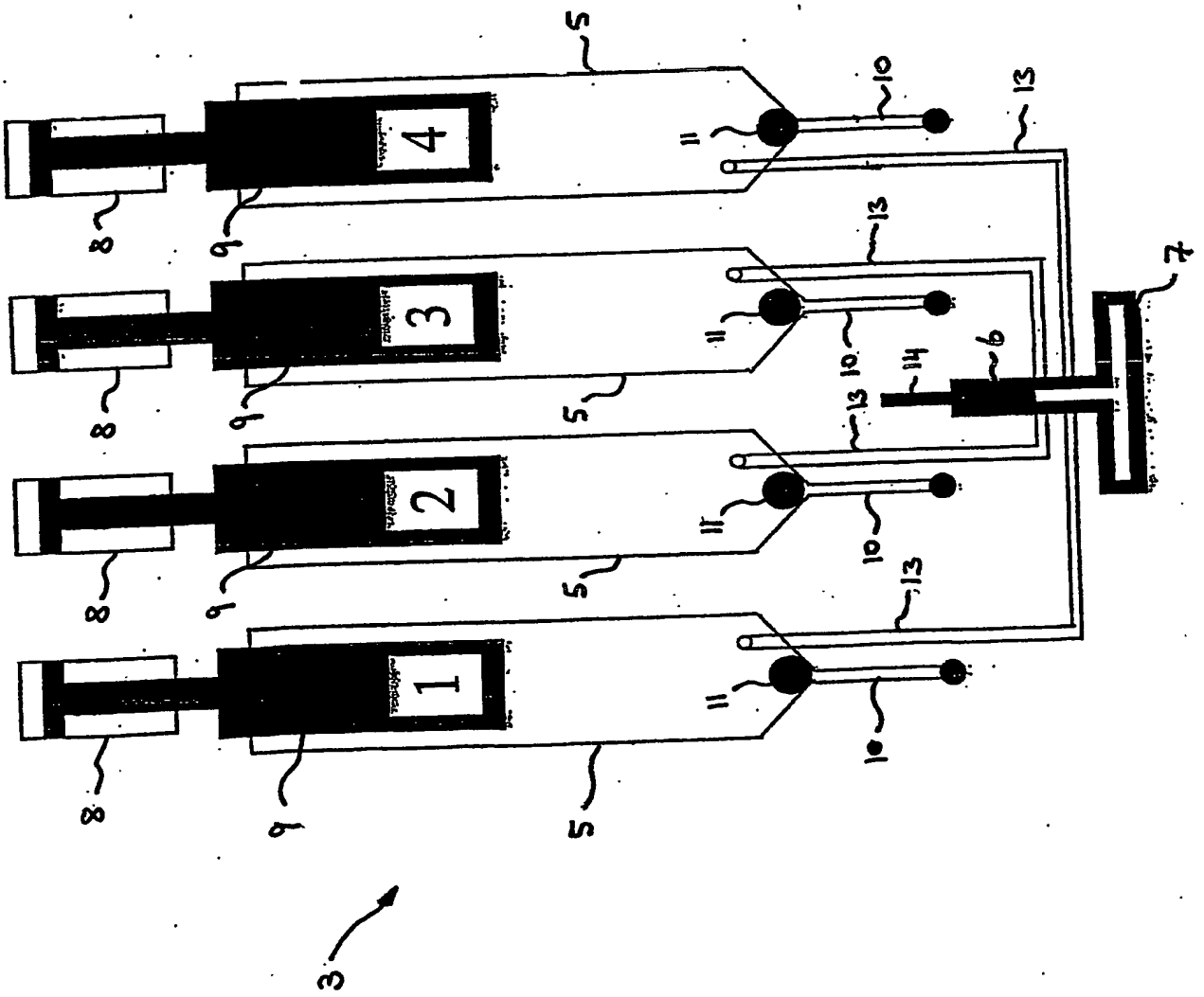
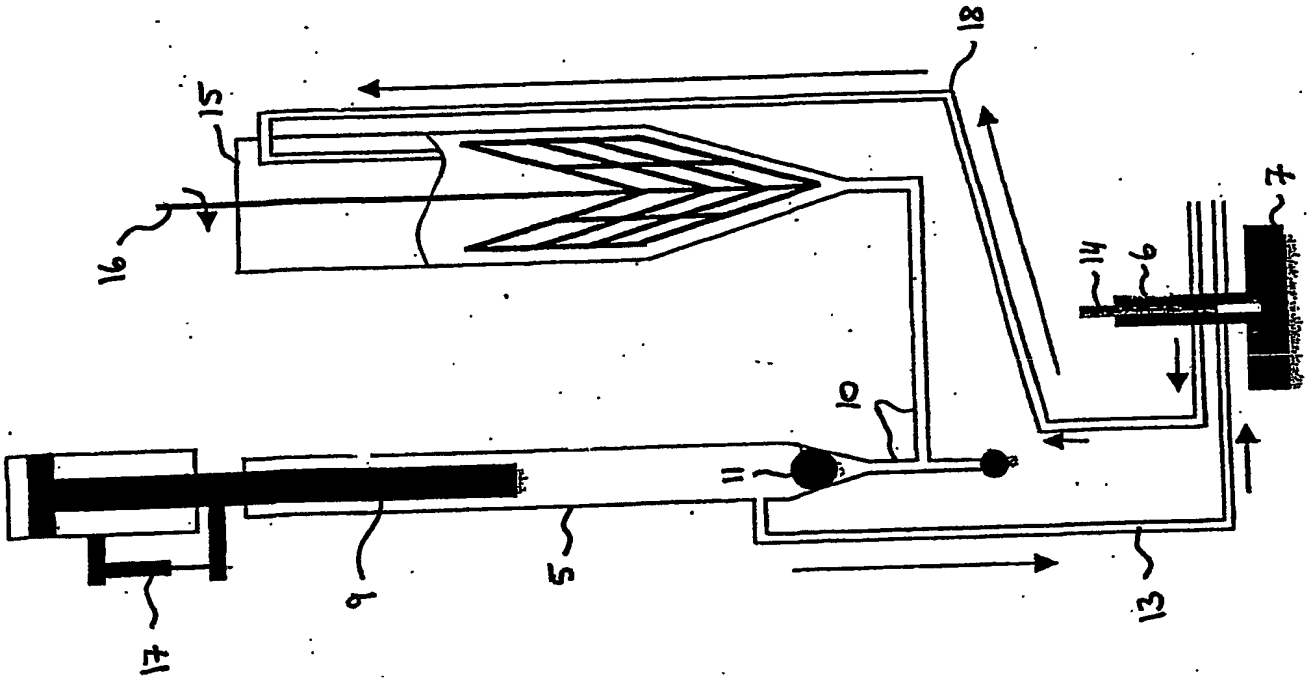


FIGURE 8.



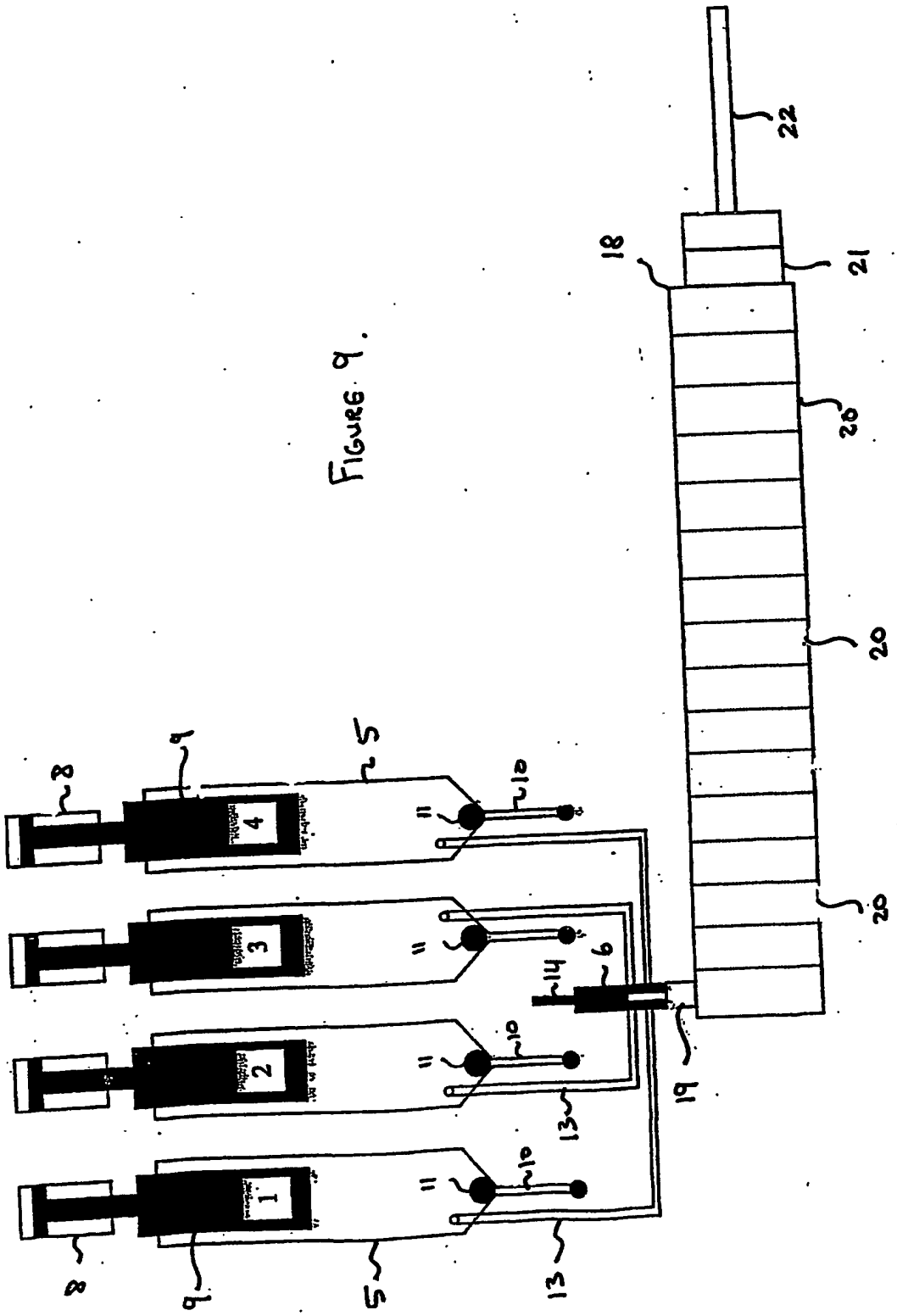


Figure 9.

PCT Application

GB0304352